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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/975,899	10/12/2001	Douglas J. Goetz	D6379	1164

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EXAMINER	
BELYAVSKYI, MICHAIL A	
ART UNIT	**PAPER NUMBER**
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/975,899	GOETZ ET AL.	
	Examiner	Art Unit	
	Michail A Belyavskyi	1644	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 15 October 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Continuation Sheet*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: 6.

   Claim(s) withdrawn from consideration: _____.

8. ☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☐ Other: _____

Continuation of 5. does NOT place the application in condition for allowance because: Claim 6 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Hallahan (US Patent NO: 6,159,443) in view of WO 98/53852 , the know fact disclosed in the specification on pages 4, lines 3-20 ; 5, lines 1-5; and 10, lines 12-20 Mastrobattista et al.,(Biochim. Biophys. Acta, 1999, 1419, 353-363) and Patel et al (FASEB 1998, Vol.12 pages 1447-1454) for the same reasons set forth in the previous Office Action, mailed on 08/25/04.

Applicant's arguments, filed on 10/15/04 have been fully considered, but have not been found convincing.

Applicant asserts that: (i) Mastobattista et al only teaches targeting immunoliposomes to epithelial cells in vitro not in vivo; (ii) US Patent '443 only teaches of a selectively targeting tumors by delivering radiation to target and also disclosed microspheres or liposomes as bio-compatible particles, that is not a partical of biodegradable polymer or PEGylated copolymer as claimed in the amended claim 6;

Contrary to Applicants's assertion US Patent '443 teaches a method of treating cancer , the method comprising steps of exposing a target tissue or organ to the ionizing radiation and administering P-selectin antibody labeled delivery vehicle that carry active agent to the tumors (see entire document, Abstract , column 6, lines 5-30 and column 13, lines 24-30 in particular). US Patent '443 teaches radiation -induced increase in P-selectin in irradiated tumor and that the present invention contemplate the selective targeting of tumors by delivering radiation to target tumors and using a delivery vehicles which bind to P-selectin. The use of radiation to control cellular adhesion molecules is a unique approach to the treatment of tumors (see column 6, lines 5-15 in particular). US Patent '443 teaches that delivery vehicle is a biodegradable particles bearing antibodies that specifically bind to a P-selectin (column 7-8 in particular). Applicant's attention is drawn to column 7, lines 45-65 that specifically disclosed biodegradable particle such as microspheres or liposomes as delivery vehicles. It is noted that the specification as filed disclosed liposomes as the examples of biodegradable particle (see page 11 lines 3-20 in particular).

Applicant's argues that US Patent '443 does not teach that P-selectin in expressed on an endothelial cell of irradiated tissue. However, this functional limitation would be obvious result of the effects of the ionizing radiation on irradiated tissue or organ taught by US Patent '443 because both the prior art and the instant invention administer the same treatment i.e. exposing a target tissue or organ to the ionizing radiation. Moreover, the specification clearly disclosed that it was known at the time the invention was made that P-selectin translocated to the cell membrane of endothelial cells within 30 minutes post irradiation (see page 9, lines 3-10 in particular) . Therefore it would be obvious to one of ordinary skill in the art at the time the invention was made to conclude that P-selectin would be in endothelial cells in irradiated tumors.

The claimed invention differs from the reference teaching in that US Patent '443 does not teach a particle of biodegradable polymers or PEGylated copolymers comprising antibodies that binds to ICAM-1.

WO'852 teaches that exposure tissue to irradiation causes an increase in expression of several cell adhesion molecules including ELAM-1, E-selectin and ICAM-1, in endothelial cells (see entire document, page 2, lines 15-25 and page 3, lines 1-10 in particular).

The known fact disclosed in the specification on pages 4, lines 3-20 ; 5, lines 1-5; and 10, lines 12-20 teaches that it has been known for over 15 years that exposure of normal and diseased tissue to irradiation causes an increase leukocyte infiltration and that the key component of this process is the adhesion of leukocytes to the microvascular endothelium. In response to biochemical stimuli the endothelium become activated and increases its expression of receptors of several cellular adhesion molecule including E-selectin, P-selectin and ICAM-1.

Mastrobattista et al. teach biomolecular carrier, bearing anti ICAM-1 antibodies (see entire document, Abstract in particular). With regards to issue that Mastrobattista et al., target anti-ICAM-1 immunoliposomes in vitro not in vivo. It is noted that Mastrobattista et al. clearly stated that biomolecular carrier, bearing anti ICAM-1 antibodies can be effectively used to delivery drugs to the sites where the expression of ICAM-1 is increased (see Abstract in particular).

Patel et al., teaches a generation a particle of biodegradable polymer or PEGylated copolymer as a new type of drug carrier (see entire document, Abstract in particular). Patel et al., teaches that one of the advantage of using said particles is that they are not rapidly removed from the circulation (see page 1448 in particular).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of WO'852, Mastrobattista et al., , known fact disclosed in Specification on pages 4, 3-20 ; 5, lines 1-5; and 10, lines 12-20 and Patel et al., to those of US Patent ' 443 and substitute biomolecular carrier bearing antibodies to one cellular adhesion molecule i.e. P-selectin to another type of particle of biodegradable polymers or PEGylated copolymers carrier bearing antibodies to another cellular adhesion molecule i.e. ICAM-1, since the expression of any one of them would be enhanced in target tissue after irradiation, to obtain a claimed method of treating cancer, comprising the steps of irradiating a target tissue or organ and administering the biomolecular carrier bearing antibodies that specific to ICAM-1.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because it has been known for over 15 years that exposure of normal and diseased tissue to irradiation causes an increase leukocyte infiltration and that the key component of this process is the adhesion of leukocytes to the microvascular endothelium, as taught by the known fact disclosed in the specification on pages 4, lines 3-20 and exposure tissue to 2irradiation causes an increase in expression of several cell

adhesion molecules including ELAM-1, E-selectin and ICAM-1, in endothelial cells, as taught by the WO'852 and P-selectin labeled delivery vehicle was used to delivery drugs to target cancer tissue or organ where the expression of this cell adhesion molecule was increased by exposure said tissue or organ to irradiation, as taught by US Patent '433 and biomolecular carrier, bearing antibodies to another cell adhesion molecules ICAM-1 effectively used to delivery drugs to the sites where the expression of ICAM-1 is increase, as taught by Mastrobattista et al. In addition, using a particle of biodegradable polymer or PEGylated copolymer as a new type of drug carrier is more advantage because they are not rapidly removed from the circulation as taught by Patel et al.

With regard to the issue that liposomes as bio-compatible particles is not a partical of biodegradable polymer or PEGylated copolymer as claimed in the amended claim 6.

It is noted that Applicant himself acknowledge that biogedradable particles are only one kind of drug carrier. Other classes of carriers include liposomes and microbubbles are known in the art and can be adapted to target a specific cell or tissue (see Applicant's arguments, filed on 07/22/04, overlapping pages 9 and 10 in particular). Said statement supports the Examiner position that it would be obvious to a person of ordinary skill in the art at the time the invention was made to substitute one type of biomolecular carrier i.e. immunoliposomes comprising antibodies that binds to ICAM-1 with another type of biodegradable particles, i.e. particle of biodegradable polymers or PEGylated copolymers, as taught by Patel et al. As has been acknowledge by the Applicant , the combined prior art teaches a method of treating a cancer in an individual comprising irradiating a target tissue and administering an anti-ICAM-1 immunoliposome (see Applicant's arguments, filed on 07/22/04, page 10 in particular).

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

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